REMARKS

After amendment, the pending claims are 1, 4-10, and 12-13. Claims 2 and 14 have been canceled without prejudice. Claim 1 has been amended to incorporate the features of now-cancelled claim 2. The remaining claims have been amended to refer to the antisense oligonucleotide recited in amended claim 1. No new matter is added by these amendments.

Any subject matter canceled from the claims by amendment is reserved for refiling in a continuation application filed during the pendency of this application.

Applicants hereby affirm the correctness of the inventive entity in view of the cancellation of the claims and that the subject matter of the pending claims was commonly owned at the time the invention was conceived.

The specification was amended to correct grammatical errors and to clarify trademark usage. No new matter is added by these amendments.

Information Disclosure Statement

The Examiner has asserted that documents AD and BQ were not considered since the same are in a foreign language and no translations were provided.

Applicants respectfully request reconsideration of the consideration of documents AD and BQ for the following reason.

According to 37 CFR § 1.97(3)(i), Applicants provided a concise explanation of the relevance of the document (AD) in the Supplemental Information Disclosure

Statement filed March 31, 2003. Applicants also provided an ***English language*** abstract of document AD as document BQ.

In view thereof, Applicants respectfully request that the Examiner consider documents AD and BQ.

Rejection under 35 USC §103(a)

> The Examiner has rejected claims 1, 2, 4-10, and 12-14 as being allegedly made obvious under 35 USC § 103(a) by International Patent Publication No. WO 99/67368 (Cases) in view of US Patent No. 6,613,567 (Bennett) and Fritz *et al*, **1997** *J. Coll. Interface Sci., 195*:272-288 (Fritz).
>
> The Examiner has asserted that it would have been prima facie obvious for one of skill in the art to have made and used antisense oligonucleotides targeted to a coding region of SEQ ID NO:3 of Applicants' invention using SEQ ID NO: 2 of Cases and the method of Bennett. The Examiner states that one of skill would have been motivated to modify the antisense oligonucleotides since Bennett and Fritz teach antisense oligonucleotides with modified bases that confer increased nuclease resistance, increased uptake in cells, and increased binding affinity for an mRNA target. Further the examiner states that 40% inhibition would have been expected based on Bennett and Fritz' disclosures.

Applicants respectfully request reconsideration and withdrawal of this rejection for the following reason.

The combination of Cases, Bennett and Fritz does not provide a reasonable expectation of success sufficient to make a *prima facie* case of obviousness of Applicants' claimed invention. Cases refers to nucleic acid compositions encoding acyl CoA:cholesterol acyltransferase (ACAT) polypeptides, the polypeptide products (e.g., ACAT-2) produced thereof, and methods of

making the same. Cases also provides the coding sequence of the human ACAT-2 gene as SEQ ID NO:2.

The Examiner has asserted that SEQ ID NO:2 of Cases is identical to SEQ ID NO:3 of Applicants' invention. However, Applicants note that these sequences are not identical. Specifically, SEQ ID NO:2 of Cases contains 1509 nucleotides, while SEQ ID NO:3 of Applicants' invention contains 1569 nucleotides.

As admitted by the Examiner, Cases does not a compound targeted to a coding region of a nucleic acid molecule encoding acyl CoA cholesterol acyltransferase-2 that hybridizes with and inhibits expression of human acyl CoA cholesterol acyltransferase by at least 40% or such antisense oligonucleotides modified as specified by the present dependent claims.

Bennett and Fritz are cited for "generic" teachings related to antisense compounds. Neither is directed to antisense oligonucleotides to ACAT-2.

Applicants, with respect, rebut the examiner's conclusion that with regard to ACAT-2, this cited art provides an ***expectation of success*** in obtaining antisense oligonucleotides capable of inhibition expression of ACAT-2 by 40%.

There is no way for anyone of skill in the art to predict whether one may obtain any particular percentage of inhibition simply by prior knowledge of generic antisense technology, (i.e., that fact that for completely unrelated genes, high levels of expression have been obtained), coupled with a known target sequence. Applicants' respectfully submit that there is nothing ***in this combination of prior art*** that suggests

such success ***with ACAT-2 would be expected***. One of skill might be motivated to "hope for" such a level of success using generic technology. However, nothing in the prior art allows for such an expectation. Only the present invention identifies that antisense oligonucleotides to ACAT-2 may be provided that inhibit expression by at least 40%. In fact, as evidenced by Tables I and I of the present specification, it is likely that one might look for an antisense sequence to ACAT-2 and find sequences that do not inhibit at all or that inhibit by considerably less than 40%.

None of the cited art provides any direction at all to indicate what sequences, if any, may be characterized by such a claimed level of inhibition of ACAT-2. Cases provides no direction at all regarding level of inhibition of ACAT-2. Fritz's discussion of carriers for oligonucleotides is not at all directed to inhibition level at all. The results of antisense studies in Bennett, show that only 12 of 39 tested oligonucleotides and 31 of 39 tested oligonucleotides that hybridized to the unrelated gene HER-2, were able to meet that level of inhibition. This result with HER-2 does not permit one of skill in the art to be able to predict Applicants' results with antisense sequences to ACAT-2, in which 15 of 23 oligonucleotides tested resulted in oligonucleotides meeting the required inhibition level of 40%.

There is no way to predict what target sequences the person of skill in the art would have used to generate results, and thus no way to predict Applicants' results *a priori*. For example, if the person of skill in the art,

for example, performed generic antisense technology techniques on Cases' sequence, that person may have obtained Applicants' SEQ ID NOS: 40, 50 or 55, which demonstrate little inhibition.

In fact, Applicants' assignee, which is a company that specializes in antisense technology and uses the latest in bioinformatics programs, have demonstrated repeatedly that one may investigate 80 or more oligonucleotides in attempts to identify a target site permitting inhibition at a specific high level for a specific gene. One cannot anticipate similar results when one looks at completely different genes. One of skill in the art cannot *a priori* expect ease of target identification simply by knowing antisense methodologies and the gene sequence.

None of these references, taken alone or together, teach or suggest a compound 8 to 50 nucleobases in length targeted to a nucleic acid molecule encoding ***ACAT-2*** (SEQ ID NO: 3), which specifically ***hybridizes with and inhibits*** the expression of ACAT-2 ***by at least 40%,*** as required by the present claims.

To make an obviousness rejection, the examiner may review the combined teachings of the cited prior art, knowledge of one of ordinary skill in the art, and the nature of the problem to be solved as a whole.[1] However, the courts have held that this range of sources does not diminish the requirement for actual evidence. Broad conclusory statements regarding the teaching of multiple

---

1 Citing *In re Kotzab*, 217 F. 3d 1365, 1370, 55 USPQ2d 1313, 1317 (Fed. Cir. 2000)

references, standing alone, are not evidence.[2] Such a showing must be clear and particular.

With respect, no such clear and specific suggestion is made by the above combination that would make obvious the composition of claim 1 and its dependent claims. First, claim 1 and its dependent claims recite a ***specific*** gene, ACAT-2, as well as antisense oligonucleotides having a specific minimum inhibitory effect. Taking each reference as a whole, this combination does not provide any *suggestion* of the composition of claim 1.

The combination of these references does not provide any *expectation of success* that if one did target the ***specifically claimed*** ACAT-2 SEQ ID NO: 3 sequence of the present claims, that one would obtain antisense sequences that are capable of inhibiting expression of the gene by at least 40%. The only source of the required motivation to make and use antisense compounds directed to specific sequences of ACAT-2 is provided by the Applicants' own specification. The only teachings that supply any expectation of success with respect to ACAT-2 are provided by the instant specification. Obtaining the motivation for combination of the prior art cannot properly be provided by Applicants' own disclosure.

---

2 See, e.g., *In re Dembiczak*, 50 USPQ2d 1614, 1616-1617 (Fed. Cir. 1999): "Our case law makes clear that the best defense against the subtle but powerful attraction of a hindsight-based obviousness analysis is rigorous application of the requirement for a showing of the teaching or motivation to combine prior art references. ... Combining prior art references without evidence of such a suggestion, teaching, or motivation simply takes the inventor's disclosure as a blueprint for piecing together the prior art to defeat patentability - the essence of hindsight. ..."; and In re Lee, 277 F.3d 1338, 1342-44, 61 USPQ2d 1430, 1433-34 (Fed. Cir. 2002).

Applicants maintain that the combination of the cited prior art, when the teachings are taken *as a whole*, fails to supply both clear and specific suggestions and evidence which provide both motivation ***and a reasonable expectation of success*** required to set forth obviousness of the pending claims.

In view of the above amendments and these remarks, Applicants respectfully request that the examiner withdraw the outstanding rejections and permit the above pending claims to pass to issue in due course.

Reconsideration of this rejection is requested.

The Director is hereby authorized to charge any deficiency in any fees due with the filing of this paper or credit any overpayment in any fees to our Deposit Account Number 08-3040.

Respectfully submitted,

HOWSON AND HOWSON
Attorneys for Applicants

By Mary E. Bak

Mary E. Bak
Registration No. 31,215
Spring House Corporate Center
Box 457
Spring House, PA 19477
(215) 540-9200